Remarks

Claims 25-55 were pending in the subject application. By this Amendment, claims 25, 29, 30-35, 40, 41, 43, 49, 50, and 52 have been amended, claims 28, 36, 37, 42, 44, and 51 have been cancelled, and claims 56-63 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 25-27, 29-35, 38-41, 43, 45-50, 52-62 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicants have submitted with this Amendment formal drawings in response to the Notice of Draftsperson's Patent Drawing Review. Figure 1A has been amended to insert the label "Sertoli-Sertoli junctional complex". Support for this amendment can be found, for example, at page 14, lines 1-4, of the subject specification. The applicants submit that no new matter is incorporated into the formal drawings. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Pursuant to the Draftperson's Review, certain textual matter has been deleted from the figures and inserted into the Description of the Drawings section at pages 11 and 12 of the subject specification.

Claims 40-55 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite. The applicants respectfully submit that claims 40-55 are not indefinite. However, by this Amendment, the applicants have amended claims 40 and 50 in order to lend greater clarity to the claimed subject matter.

Claim 40 recites a method of making a biochamber by co-culturing Sertoli cells and non-Sertoli cells in the presence of a basement membrane preparation for a period of time sufficient for the Sertoli cells to form an outer wall surrounding a plurality of the non-Sertoli cells. Claim 50 recites a method of transplantation by transplanting a biochamber into a host. The applicants respectfully submit that the currently pending claims recite affirmative (non-passive) steps for carrying out the invention.

In view of the preceding remarks and amendments to the claims, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claims 25-55 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The Office Action raises certain issues regarding the structure of the claimed biochambers and the figures of the patent application. The applicants respectfully submit that there is no discrepancy or inconsistency between the Figures and the claimed invention. However, as indicated above, the applicants have now submitted formal drawings, and the claims have been amended in order to lend greater clarity to the claimed subject matter. Claim 25 recites a biochamber comprising a lumen, an outer wall defining the lumen, and a plurality of non-Sertoli cells contained within the lumen, wherein the outer wall comprises Sertoli cells. Claim 40 recites that the biochambers are made by co-culturing Sertoli cells and non-Sertoli cells in the presence of a basement membrane preparation for a period of time sufficient for the Sertoli cells to form an outer wall surrounding a plurality of the non-Sertoli cells. Support for this amendment can be found, for example, at page 13, lines 24-30, page 14, lines 1-14, and the Examples and Figures of the application as originally filed. These features can be clearly observed in the formal drawings submitted herewith. In addition, submitted herewith is a declaration under 37 CFR §1.132 by Dr. Don Cameron, with accompanying Exhibits A-M. In his Declaration, Dr. Cameron describes the structure and functional mechanism of the biochambers of the subject invention. As indicated in Dr. Cameron's Declaration, the biochambers of the subject invention "mimic the general structure of the seminiferous epithelium *in vivo*, and it is expected that this would include the Sertoli cell monolayer structure of the blood-testis barrier." In addition, as described by Djakiew and Onada (Exhibit M), it has been observed that Sertoli cells can form confluent epithelial sheets when cultured in the presence of a basement membrane preparation, such as MATRIGEL.

In addition, submitted herewith are the Cameron *et al.* (2001) publications (Exhibits J and K), which describe the production of biochambers using methods of the subject invention, as taught in the subject specification. The publications are submitted herewith to support and verify the sufficiency of the specification as originally filed. For example, Figure 2 of Exhibit K shows a scanning electron micrograph of a biochamber with the outer wall of Sertoli cells partially fractured,

exposing the islets contained therein. The biochamber structure can also be seen in Figures 1-3 of Exhibit J, for example.

Therefore, the applicants respectfully submit that the subject specification, including Figures 1-7, demonstrate that the applicants were in possession of the claimed invention, as required by 35 U.S.C. §112, first paragraph.

In view of the remarks above and the amendments to the claims, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 25-55 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicants respectfully submit that the claimed invention is fully enabled by the subject specification. However, as indicated above, the applicants have amended the claims to lend greater clarity to the claimed subject matter.

The Office Action indicates that it is likely that the Sertoli cells that form the outer wall of the claimed biochambers would be a significant barrier for oxygen diffusion to the non-Sertoli cells contained within the lumen. However, as indicated in Dr. Cameron's Declaration, "it has long been known that there is direct diffusion of oxygen across Sertoli cells to the luminal compartment, within the seminiferous tubule. As observed in the paragraph bridging pages 486 and 487 of the Free *et al.*, *Biology of Reproduction*, 14:481-488, 1976 (submitted herewith as Exhibit L), "[t]he lumen of the seminiferous tubules is remote from the blood supply yet does not appear to have a substantially lower oxygen tension than the capillary-rich interstitial tissues" (emphasis added)." Therefore, encapsulating the non-Sertoli cells within a wall of Sertoli cells using the methods of the subject invention actually obviates difficulties with oxygen diffusion that may be encountered with other encapsulating materials.

In view of the remarks above and the amendments to the claims, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 25-30, 33-40, 42, and 46-55 have been rejected under 35 U.S.C. §102(b) as being anticipated by Selawry (U.S. Patent No. 5,843,430). The Office Action indicates that the Selawry patent describes co-culturing Sertoli cells and islet cells and transplanting the co-culture to diabetic rats. As indicated in the preceding paragraphs, in order to lend greater clarity to the claimed subject matter, the applicants have amended the claims. Claim 25 recites a biochamber having a lumen, an

outer wall defining the lumen, and a plurality of non-Sertoli cells contained within the lumen, wherein the outer wall comprises Sertoli cells. Claim 40 recites that the biochambers are made by co-culturing Sertoli cells and non-Sertoli cells in the presence of a basement membrane preparation for a period of time sufficient for the Sertoli cells to form an outer wall surrounding a plurality of the non-Sertoli cells. The Selawry patent does not teach or suggest the claimed biochambers or methods for producing or using such biochambers. Accordingly reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Claims 25-40, 42, and 46-55 have been rejected under 35 U.S.C. §102(e) as being anticipated by Sanberg *et al.* (U.S. Patent No. 5,942,437). The Office Action indicates that the *Sanberg et al.* patent describes co-culturing Sertoli cells and therapeutic cells such as islet cells, neurons, adrenal chromaffin cells, embryonic dopaminergic cells, and NT2 neuronal cells, and transplanting the co-culture to a host. As indicated in the preceding paragraphs, the applicants have amended the claims in order to lend greater clarity to the claimed subject matter. Claim 40 recites that the biochambers are made by co-culturing Sertoli cells and non-Sertoli cells in the presence of a basement membrane preparation for a period of time sufficient for the Sertoli cells to form an outer wall surrounding a plurality of the non-Sertoli cells. The Sanberg *et al.* patent does not teach or suggest the claimed biochambers or methods for producing or using such biochambers. Accordingly reconsideration and withdrawal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

Claims 25-30, 33-42, and 46-49 have been rejected under 35 U.S.C. §102(e) as being anticipated by Spaulding (U.S. Patent No. 6,001,643). The Office Action indicates that the Spaulding patent describes a method of co-culturing Sertoli cells with pancreatic islet cells using a microgravity method. As indicated above, claim 40 recites that the biochambers are made by co-culturing Sertoli cells and non-Sertoli cells in the presence of a basement membrane preparation for a period of time sufficient for the Sertoli cells to form an outer wall surrounding a plurality of the non-Sertoli cells. The Spaulding patent does not teach or suggest the claimed biochambers of the subject invention or the claimed methods for producing or using such biochambers.

As the Examiner is aware, in order to anticipate, a single reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991).

The applicants respectfully assert that the cited reference does not teach or suggest each and every element of the applicants' claimed invention. The Spaulding patent does not teach or suggest the claimed biochambers, or methods of making such biochambers by co-culturing the cells in the presence of a basement membrane preparation for a period of time sufficient for the Sertoli cells to form an outer wall surrounding a plurality of the non-Sertoli cells. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §102(e) is respectfully requested.

By this Amendment, new claims 56-63 have been added. Support for new claims 56-63 can be found within the subject specification, for example, at page 14, lines 1-14, Examples 1-3 at pages 17-20, and the figures as originally filed.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachments: Marked-up Version of Substitute Paragraphs
Marked-up Version of Amended Claims
Petition and Fee for Extension of Time
Amendment Transmittal Letter
Formal Drawings
Declaration under 37 CFR 1.132 by Dr. Cameron with Exhibits A-M

Marked-up Version of Substitute Paragraphs

[Figure 1 is a diagram] Figures 1A and 1B are diagrams showing the formation of a biochamber on a substrate. As shown in Figure 1B, apical secretion in a closed compartment creates a fluid-filled lumen by appreciating hydrostatic pressure;

[Figure 2 is a comparison showing] Figures 2A and 2B are diagrams comparing the differences between the conventional culture and a microgravity co-culture. As shown in Figure 2A, apical secretion in a closed compartment creates a fluid-filled lumen by appreciating hydrostatic pressure. As shown in Figure 2B, microgravity coculture results in the integration of therapeutic cells into Sertoli cell biochambers;

Figure 3 is a mechanism showing the way the Sertoli cells effect immunosuppression at the graft site. Positive FasL immunostatining identifies Sertoli cells and suggests a mechanism by which they may effect immune suppression at the graft site. The expression of FasL by Sertoli cells induces apoptosis of the invading immune cells by binding to the upregulated Fas receptors on these activated T-lymphocytes. This results in the attrition of these immune cells at the graft site thereby down-regulating the immune responses-this by an already well-defined mechanism occurring naturally in the mammalian system;

Figure 6 is a photograph of Sertoli-Neuron-Aggregate-Cells (SNACS) for in vitro following co-culture of rat Sertoli cells and NT2 neurons in simulated microgravity utilizing the High Aspect Rotation Velocity (HARV) bioreactor (1 week HARV co-culture); and

Figure 7 is a photograph of immunocytochemical staining of mouse FasL and human nuclear matrix proteins in Sertoli-Neuron Aggregated Cells (SNACs) following HARV incubated co-cultures (1 week HARV co-culture).

Marked-up Version of Amended Claims

25. A biochamber comprising [a lumen and an outer wall, wherein said outer wall comprises Sertoli cells and defines said lumen] a lumen, an outer wall defining said lumen, and a plurality of non-Sertoli cells contained within said lumen, wherein said outer wall comprises Sertoli cells.

29. The biochamber according to [claim 28] claim 25, wherein said plurality of non-Sertoli cells are selected from the group consisting of neuronal cells, NT2 cells, pancreatic islet cells, dopaminergic cells, and bovine chromaffin cells.

30. The biochamber according to [claim 28] claim 25, wherein said plurality of non-Sertoli cells comprises pancreatic islet cells.

31. The biochamber according to [claim 28] claim 25, wherein said plurality of non-Sertoli cells comprises neuronal cells.

32. The biochamber according to [claim 29] claim 31, wherein said neuronal cells are NT2 neurons.

33. The biochamber according to [claim 28] claim 25, wherein said plurality of non-Sertoli cells comprises secreting cells.

34. The biochamber according to [claim 28] claim 25, wherein said plurality of non-Sertoli cells includes at least one therapeutic cell.

35. The biochamber according to [claim 28] claim 25, wherein said Sertoli cells of said outer wall provide immunoprotection to said plurality of non-Sertoli cells within said lumen upon transplantation of said biochamber.

40. A method of making a biochamber comprising [the steps of]:

[co-culturing Sertoli cells and non-Sertoli cells; and

organizing the Sertoli cells and the non-Sertoli cells, wherein the Sertoli cells form an outer wall defining a lumen, and wherein the non-Sertoli cells are contained within the lumen]

co-culturing Sertoli cells and non-Sertoli cells in the presence of a basemement membrane preparation for a period of time sufficient for the Sertoli cells to form an outer wall that encapsulates a plurality of the non-Sertoli cells.

41. The method according to claim 40, wherein said co-culturing [step] is carried out under microgravity conditions.

43. The method according to [claim 42] claim 40, [wherein said segregating step comprises inducing the] wherein the basement membrane preparation causes epithelization and polarization of the Sertoli cells, thereby inducing the Sertoli cells to form the outer wall that encapsulates the plurality of non-Sertoli cells.

45. The method according to [claim 44] claim 40, wherein the [compound comprises a solubilized] basement membrane preparation comprises MATRIGEL.

49. The method according to claim 40, wherein the [Sertoli cells are arranged as a monolayer following said organizing step] outer wall comprises a monolayer of Sertoli cells.

50. A method of transplanting cells comprising the steps of:

[forming a biochamber comprising an outer wall of Sertoli cells and a lumen, wherein the outer wall defines the lumen;

incorporating non-Sertoli cells into the lumen of the biochamber; and

transplanting the biochamber containing the non-Sertoli cells into a host]

transplanting a biochamber into a host, wherein the biochamber comprises a lumen, an outer wall defining said lumen, and a plurality of non-Sertoli cells contained within said lumen, wherein said outer wall comprises Sertoli cells.

52. The method according to claim 50, wherein the [Sertoli cells are arranged as a monolayer] outer wall comprises a monolayer of Sertoli cells.